A TWIN STUDY ON THE HERITABILITY OF LIPOPROTEIN FRACTIONS

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Volunteer adult twins (aged 18-65), after a 12-hour fast, provide two 15 ml samples of blood for analysis by Auto Analyzer II, by agarose electrophoresis and by direct gas chromatography. Provisional diagnosis of zygosity is based on subjects' own opinions, supported by dermatoglyphic analysis and, in any difficult case, substantiated by an enzymatic series. Analysis of the AA-II and electrophoresis data on the first 2 × 45 subjects shows a significant positive correlation within MZ pairs for each of the 7 lipid measurements considered, while the estimate of correlation within DZ pairs is lower in every case. Heritability appears to be higher for cholesterol than for triglyceride fractions. The electrophoretic band for the sinking pre-beta lipoprotein fractions has behaved like a simple genetic marker. Interrelationships among different lipoprotein fractions are studied in terms both of phenotypic and genetic correlations, both of which confirm the expected positive association between amounts of triglyceride and of cholesterol in the supernatant ($Sf > 20$), and both also show negative correlation between the pre-beta and the alpha fractions. Another aspect of the analysis is the study of lipid differences between MZ cotwins in relation to corresponding intrapair differences in body weight and medical history; male, but not female pairs, show a measurable statistical dependence of cholesterol and triglyceride levels on « excess » body weight.

The Toronto Twin Register is a recently established volunteer panel among whose members we hope to find subjects suitable for, and willing to participate in, a variety of biomedical research projects. Its first two " outside " clients were an investigator who needed twin subjects for the study of variation in the rates of drug clearance, and another who is studying genetic factors affecting susceptibility to bronchitis. As an initial project, for which twins could volunteer at the time of registration, we chose to study the heritability of lipoprotein fractions and interrelations among them. We were able to take advantage of the circumstance that Toronto has both a specialized lipid chemistry laboratory participating in the Lipid Research Clinics program of the U.S. National Heart and Lung Institute, for which it conducts highly reliable analyses of blood both by Auto Analyzer II and by agarose electrophoresis, and another automated facility employing direct gas chromatography capable of quantifying by simultaneous determination all of the plasma lipids.

This study is restricted to adult subjects who, after a 12-hour fast, provide two 15 ml samples of blood, one for each of the participating laboratories. It is intended to enter at least 100 pairs of twins into the study, but this present progress report can employ measurements of only 2 × 45 subjects. Moreover, the total number of complete lipoprotein profiles so far prepared by the Toronto laboratories is about 300, with quite small samples in certain age/sex groups, so that the twin measurements have not yet been transformed to an age-adjusted basis.

Table 1 confirms that a statistically significant resemblance between MZ twins in respect of each lipid fraction is demonstrable from as few as 28 pairs. This resemblance appears to be somewhat stronger for cholesterol than for triglycerides. The result for sinking pre-beta is particularly striking, the first 28 MZ pairs being 100% concordant for this characteristic. It should be explained that sinking pre-beta, which will eventually be quantified, is at present only noted as detected or not detected by a test sensitive to amounts in excess of 1 mg %. Forty of the first 90 twin subjects were positive by this test, a prevalence of 44%.

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Table 1. *Estimates of the correlation between adult twins in respect of certain lipid values*

	First 28 MZ pairs	First 17 DZ pairs
Total serum cholesterol	0.836	0.429
VLDL (pre-β)	0.600	0.149
LDL (β)	0.809	0.503
Sinking pre-β	1.000	0.292
HDL (α)	0.841	0.592
Total serum triglycerides	0.649	—0.047
TG in lipoprotein of $Sf > 20$	0.674	—0.138
TG in lipoprotein of $Sf < 20$	0.533	0.140
Total phospholipids	0.69[a]	0.52[b]
Critical value of r for 5% significance level:	0.375	0.482

[a] Based on 20 pairs. [b] Based on 8 pairs.

Table 2. *Estimates of the heritability of certain lipid fractions derived from two small series of adult twins*

	Toronto, Present Study, first 45 pairs	Oslo, Heiberg, 50 pairs
Total serum cholesterol	0.67	0.72
VLDL (pre-β)	0.28	0.54
LDL (β)	0.29	0.33
Sinking pre-β	1.00	....
HDL (α)	0.75	0.50
Total serum triglycerides	0.29[a]	0.50
TG in lipoprotein of $Sf > 20$	0.28[a]	....
TG in lipoprotein of $Sf < 20$	0.34[a]	....
Phospholipids	0.83[b]	0.56

[a] Based on log. values. [b] Based on 28 pairs.

The correlations between DZ twins are uniformly lower that those between MZ pairs, which suggests that there is a measurable degree of heritability for all these lipoprotein fractions.

The heritability estimates as they now stand are displayed in Table 2, together with corresponding estimates from a recently reported Norwegian study*. It will be seen that the two studies agree in suggesting a lower degree of heritability for triglycerides than for cholesterol. We consider that any confirmed indication of differences in heritability would have a practical bearing on public policy and health education programs, since these need to identify and work on the less heritable risk factors, those that may be more readily influenced by modification of "lifestyle".

A homely example of relationship between lifestyle and lipid level emerges when we inspect the intrapair differences in (stated) body weight. Fig. 1, which relates to male MZ pairs only, reflects a tendency for the more obese member of a genetically identical pair to have the higher triglyceride level and suggests a rough equivalence between 1 kg of "excess" weight and an increment of 8-10 mg % of VLDL in the serum. In this example of the so-called cotwin control method, body weight has been interpreted as an index of "environmental" exposure, rather than as a variable that is itself under a considerable measure of genetic control. The justification for this, of course, is that the weight differences considered are those between MZ cotwins and thus by definition are of nongenetic origin. It also seems relevant that the heritability of reported body weight, as estimated from data collected within this study, is very low (0.01), although that for reported height is quite substantial (0.65). When, as in Fig. 2, we come to interrelationships among the various lipoprotein fractions, there is a fairly strong presumption that the patterns of association found — whether they take the form of a positive or a negative correlation — are determined by inherited factors. In Fig. 2 the upper number of each pair is a coefficient of genetic correlation (the "cross" covariance between two different lipoprotein fractions divided by the geometric mean of their "direct" covariances). Genetic correla-

* Heiberg A. 1973. Heritability of serum lipids and lipoproteins. Paper presented at the Third International Symposium on Arteriosclerosis. Berlin, 1973.

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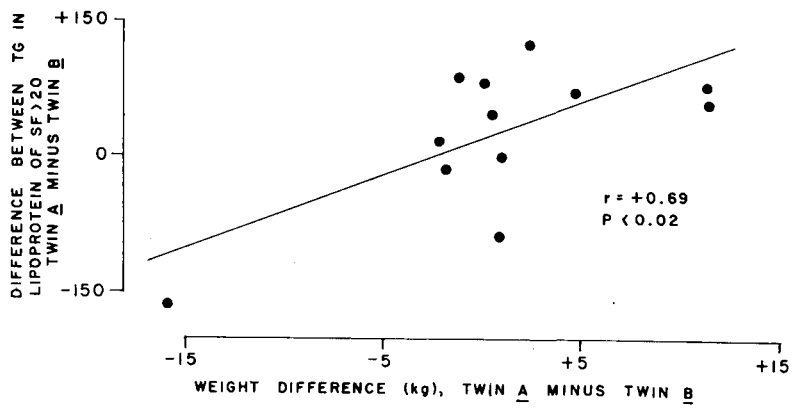
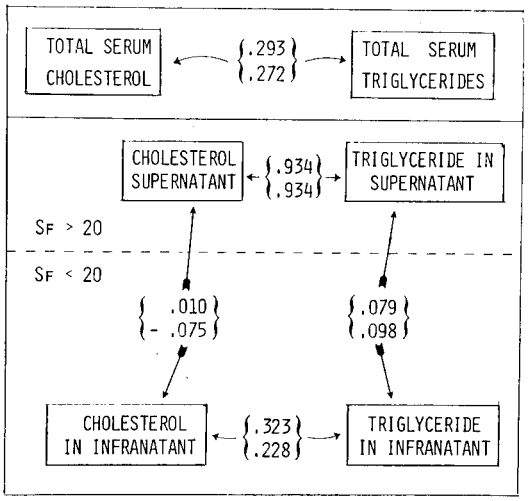


Fig. 1. Correlation between « excess » weight and elevation of triglycerides in 12 pairs of MZ twins.

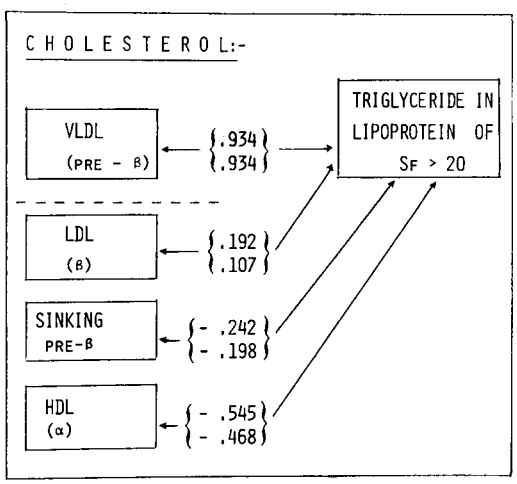


UPPER FIGURE (BASED ON 28 MZ PAIRS):-

$$Cov(x_{1I}x_{2J})/\sqrt{Cov(x_{1I}x_{2I})Cov(x_{1J}x_{2J})}$$

LOWER FIGURE (BASED ON 56 INDIVIDUAL SUBJECTS):-
CONVENTIONAL CORRELATION COEFFICIENT.

Fig. 2. « Genetic » correlations among different lipoprotein fractions.



UPPER FIGURE (BASED ON 28 MZ PAIRS):

$$Cov(x_{1I}x_{2J})/\sqrt{Cov(x_{1I}x_{2I})Cov(x_{1J}x_{2J})}$$

LOWER FIGURE (BASED ON 56 INDIVIDUAL SUBJECTS):-
CONVENTIONAL CORRELATION COEFFICIENT.

Fig. 3. « Genetic » correlations among different lipoprotein fractions.

tions have more usually been estimated from parent-offspring or from sib data, but twin data must be at least equally suitable for this purpose and the results may be easier to interpret. The estimates on this figure are based on the first 28 MZ pairs of our series; measurements on the 56 individual members of these pairs have also been used as the data for conventional phenotypic correlations which are shown as the lower figure of each pair.

The horizontal broken line represents separation by centrifuge at the level of $Sf \leqq 20$. The very high genetic correlation above this line merely reflects the fact that cholesterol and triglyceride are present in VLDL in an almost fixed ratio. Below the line there is also some positive association between the amounts of cholesterol and of triglyceride, but the feature of the diagram is the near-zero correlation

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between the supernatant and infranatant fractions. This is explored further in Fig. 3, which distinguishes three components of cholesterol within the infranatant ($Sf < 20$). It will be seen that, as we proceed down the scale of increasing density, the genetic correlation passes from a very large positive value, through low positive and low negative values, to a fairly substantial negative correlation. This inverse relationship has a plausible biochemical explanation that we do not propose to develop here. It is our hope that a knowledge of these genetic correlations will be of assistance in setting up a general typology of lipid constitutions, including perhaps the several conditions now referred to as " familial hyperlipoproteinemias ".

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